ORIGINAL ARTICLE

Behçet disease: a rare systemic vasculitis in Poland

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KEY WORDS

Behçet disease, epidemiology, morbidity, rare disease

ABSTRACT

INTRODUCTION Behçet disease (BD) is an immune-mediated small-vessel systemic vasculitis, which is rarely seen in Poland.

OBJECTIVES The aim of this study was to evaluate the incidence and prevalence of BD, as well as to assess the sex and geographical distribution of BD in Poland during a 7-year follow-up. To our knowledge, this is the first evaluation of this rare disease in Poland, based on a hospital morbidity database.

PATIENTS AND METHODS We analyzed population-based administrative data obtained from a national hospital morbidity study conducted between January 2008 and December 2014 by the National Institute of Public Health in Poland. The annual incidence rates and point prevalence of BD were calculated using the number of patients with BD and corresponding census data for the overall Polish population.

RESULTS Data included 316 hospitalization records. The final study sample comprised 130 patients (54 men [42%] and 76 women [58%]) with first-time hospitalizations for BD. The mean (SD) age was 41.6 (18.7) years (95% confidence interval [CI], 38.3–44.8; range, 5–85 years). The incidence rate of BD was estimated at 0.5 per million persons per year (95% CI, 0.35–0.61). The point prevalence at the end of 2014 was 3.4 per million persons. The incidence rate of BD did not vary significantly between more urban and more rural regions, and BD was observed more often in women than in men.

CONCLUSIONS BD is endemic in Eastern and Central Asian countries, but is also seen in Poland. However, its incidence and prevalence rates are lower in Poland than in other European countries.

INTRODUCTION Behçet disease (BD) is an immune-mediated variable vessel vasculitis that often presents with mucous membrane ulceration and ocular problems. As a systemic disease, it can also involve visceral organs such as the gastrointestinal tract, as well as the pulmonary, musculoskeletal, cardiovascular, and neurological systems. BD affects numerous bodily systems, with ocular complications often being the most devastating for the patient and his or her quality of life. It usually occurs around the third decade of life and has a chronic course with unpredictable exacerbations and remissions. The syndrome can be fatal owing to ruptured vascular aneurysms or severe neurological complications.[1] Oral and genital ulcers are among the hallmarks of BD, and patients with these signs require close surveillance for other manifestations of the disease.[2]

Several sets of diagnostic criteria had been used until 1990 when the International Study Group (ISG) for Behçet's Disease proposed a new set of criteria for diagnosis, which require the presence of recurrent oral ulcers plus 2 of the 4 additional criteria: recurrent genital ulcers, skin lesions, uveitis, or a positive pathergy test result. Owing to low sensitivity of the ISG criteria, the new International Criteria for Behçet's Disease were established and presented in 2006 at the International Conference of Behçet's Disease in Lisbon, Portugal.[3] A comparison of the 2 classification systems revealed that the latter had higher sensitivity,

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and accuracy for diagnosis in the Far East (China), Middle East (Iran), and Europe (Germany).[3]

In 2014, the International Team for the Revision of the International Criteria for Behçet's Disease, representing 27 countries, submitted data from 2556 patients with a clinical diagnosis of BD and 1163 controls with diseases mimicking BD or presenting at least 1 major sign of BD. The new proposed criteria showed a much higher sensitivity than the ISG criteria, while maintaining reasonable specificity.[4] The classification of pediatric BD for future therapeutic trials has also been recently proposed.[5]

Epidemiology of Behçet disease BD is endemic in countries of Eastern and Central Asia, especially Turkey and Iran, but is rarely seen in central Europe. However, the increased number of recently observed cases worldwide suggests that the disease may be spreading from endemic areas. BD tends to be more severe in men than in women, and it was reported that systemic involvement was also higher in men.[6] Sex distribution of the disease was reported to be roughly equal.[7] However, there are some exceptions. BD shows female predominance in Korea.[8] Male sex, younger age of onset, and increased number of organs involved at diagnosis are associated with a more severe disease course and therefore require a more aggressive treatment.[7] The incidence of anterior uveitis has been found to be higher in women with BD, and that of panuveitis—in men.[9] Female patients have a better overall prognosis than male patients.[10] A younger age at onset has also been associated with a more severe disease course.[11] Panuveitis was the most common type of uveitis among both men and women with BD, although anterior uveitis was seen more frequently in women.[12] Male patients with younger age at onset and worse visual acuity at presentation have a higher risk of visual loss over time.[13] Uveitis tends to affect patients between the ages of 20 and 40 years and is the most common cause of uveitis.[14]

A male predominance of BD has been found in the Azeri population of Iran. The incidence of BD and related retinal vasculitis was found to be higher among men than women in Azerbaijan.[15] In southeastern Turkey, the male to female ratio was found to be 0.73, but no significant differences were reported between men and women for mucocutaneous findings or systemic involvement.[16]

Although BD occurs worldwide, it is most prevalent in the region along the Silk Road in Asia and the Mediterranean. The highest prevalence of BD was 420 per 100 000 inhabitants aged 12 years or older in Istanbul, Turkey.[17] In the large urban COPCORD study in Iran, BD prevalence in the population over the age of 15 years was estimated at 80 per 100 000.[18] In northern Israel, the overall prevalence of BD was 15.2 per 100 000 and was similar in men and women. Prevalence rates among the Jewish, Arab, and Druze populations were 8.6, 26.2, and 146.4 per 100 000, respectively.[19] A 2005 survey estimated the prevalence of BD in Germany at 0.72 per 100 000 overall and 4.87 per 100 000 in the municipality of Berlin. It is thought that the prevalence of BD in Berlin is the highest in Germany due to the multiethnicity of its urban population.[20]

The results of several other studies do not support an association between ethnicity and incidence of BD, suggesting instead that environmental influences may be responsible for the higher frequency of ocular manifestations and the elevated male to female ratio in patients living in Germany compared with those living in Turkey.[21] In a study conducted in a county in the Paris metropolitan area that is home to 1 094 412 adults, of whom 26% are of non-European ancestry, the overall prevalence of BD was 7.1 per 100 000 adults aged 15 years or older, whereas the prevalence rates within the populations of European, North African, and Asian ancestry were 2.4, 34.6, and 17.5, respectively.[22] The results of this study indicate that the prevalence of BD among immigrants of North African or Asian ancestry is significantly higher than that in the European-origin population and is comparable with the rates reported from North Africa and Asia.[22] Moreover, the results suggested that the risk of BD is not related to age at immigration and supported the hypothesis that BD has a primarily hereditary origin.[22]

Recent data from northern Italy indicate an estimated incidence of BD of 0.24 per 100 000 in that region.[23] In Sweden, the point prevalence of BD on January 1, 2011, was 4.9 per 100 000 adults and was higher within the population of non-Swedish ancestry (13.6 vs 2.0 per 100 000; $P < 0.001$), and also higher among men than women (6.8 vs 3.2 per 100 000; $P = 0.019$).[24] The annual incidence rate was 0.2 per 100 000 adults and was also higher among individuals of non-Swedish ancestry (0.6 vs. 0.1 per 100 000; $P < 0.001$).[24] The incidence of BD remained elevated for immigrants from high-prevalence regions even long after settling in Sweden.[24] In a population-based study in the United States, the point prevalence in 2000 was estimated to be 5.2 per 100 000. The overall annual incidence of BD between 1960 and 2005 was 0.38 per 100 000, with a higher incidence in women than in men (0.51 vs 0.26 per 100 000).[25] One study showed the presence of BD in Russia, and it was suggested that its prevalence in Central Asian people is much higher than that in White Russian.[26] There is little information regarding BD in Poland or they are case reports.[27-32] To the best of our knowledge, this is the first large epidemiological analysis of this rare disease in Poland.

The latest study reported that in patients with BD, oral aphthosis is seen in more than 95% of patients; genital aphthosis, in 60% to 90%; skin manifestations (pseudofolliculitis/erythema nodosum), in 40% to 90%; ocular manifestations (uveitis/retinal vasculitis) in 45% to 90%, gastrointestinal manifestations (diarrhea/hemorrhage/

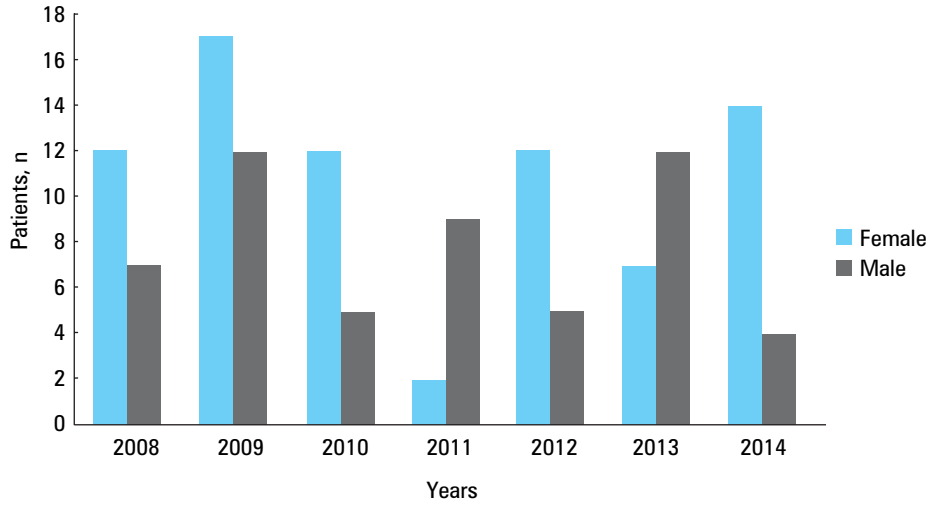

FIGURE 1 Annual number of cases of Behçet disease by sex in Poland, 2008–2014

perforation/pain), in 4% to 8%; vascular involvement (venous/arterial thrombosis, aneurysm), in 2.2% to 50%; neurological manifestations (all types, especially meningoencephalitis), in 2.3% to 38.5%); and articular involvement (arthralgia/arthritis/ankylosing spondylitis), in 11.6% to 93%.[33] The high risk of organ damage, the recurrence of BD with periods of exacerbations and remissions, the need for effective immunosuppressive therapy, and the 7-year follow-up suggest that almost all patients in this study were hospitalized during the study period, at least in the initial stage of the disease. In the Polish health care system, hospitalization is widely accepted in case of a disease requiring numerous or advanced diagnostic or therapeutic procedures. BD often requires hospitalization; therefore, the analysis of hospitalizations may provide a good estimate of the incidence. The incidence of BD may be slightly underestimated, but hospital discharge data were used for the estimation of the incidence of such vasculitides as Kawasaki disease in the United States[34] and granulomatosis with polyangiitis in Finland.[35]

The purpose of this study was to measure the incidence and prevalence of BD and to assess the differences in the sex and geographical distribution of the disease in Poland.

PATIENTS AND METHODS

This was a retrospective, population-based study that analyzed hospital discharge records with BD diagnosis. Data were obtained from the survey of the National Institute of Public Health in Poland, which covered the period from 2008 to 2014. We analyzed the records relating to the first-time hospitalizations of all patients diagnosed with BD. These data are obligatorily sent to the institute from all hospitals, except psychiatric and military ones. The data are anonymous and include information on hospitalization with ICD10-code diagnoses, date of hospital admission and discharge, birth date, sex, and the place of residence. Two analytic samples were considered in the current study: 1) all hospitalizations for BD, and 2) first-time hospitalization for BD. In addition to data from the hospital morbidity study, demographic data for the general Polish population were obtained from the Central Statistical Office of Poland.[36] The incidence and prevalence rates were calculated using the number of patients with BD and corresponding census data. The study was conducted in accordance with the generally applicable law.

Statistical analysis All statistical analyses were performed using the licensed version of the Statistica software (Dell Inc. [2016]; Dell Statistica, version 13, Tulsa, Oklahoma, United States) and WINPEPI programs.[37] The results of descriptive analyses were expressed as means, medians and ranges for continuous variables, and counts and percentages for categorical data; 95% confidence intervals (CIs) were calculated assuming the Poisson distributions of the observed cases. Nonparametric tests were used as appropriate when normality assumptions were not met. A P value of less than 0.05 was considered as statistically significant.

RESULTS

Our data included 316 hospitalization records. The final study sample comprised 130 patients with first-time hospitalizations for BD. The mean age was 41.6 years (95% CI, 38.3–44.8; range, 5–83 years). There were 54 men (41.5%) and 76 women (58.5%). BD was more often observed in women than in men (P <0.05). Based on the hospitalization records and census data, the annual incidence of BD was estimated to be 0.5 per 1 000 000 (95% CI, 0.3–0.61). The annual number of newly diagnosed cases of BD in Poland by sex during the study period is presented in FIGURE 1. There were small fluctuations in the incidence of BD during the study. The point prevalence at the end of 2014 was estimated at 3.4 per million persons. One patient died during hospitalization due to heart failure.

The age distribution of patients with BD (first-time hospitalizations) in Poland is shown in FIGURE 2. The clusters of higher absolute incidence (number of cases) were observed more frequently in urban regions than in rural regions, but the incidence rate of BD did not vary significantly between the regions.

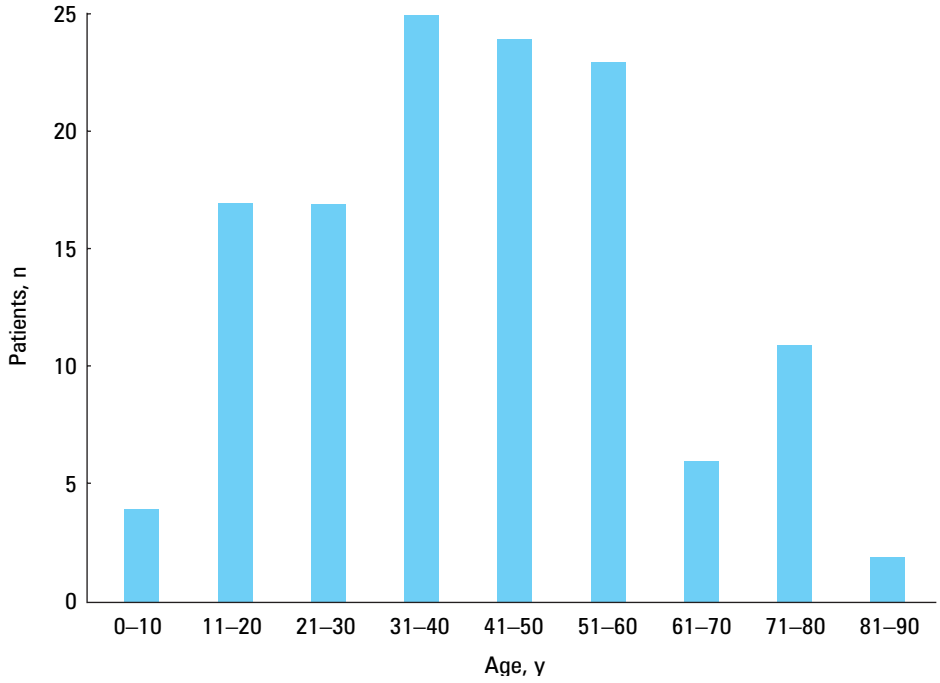

FIGURE 2 Age distribution of patients with first-time hospitalization for Behçet disease in Poland

DISCUSSION Although epidemiological data on the incidence of BD have been reported in several European countries, to our knowledge, this analysis is the first to explore the epidemiology of BD in Poland. Because BD often requires advanced diagnostic or therapeutic procedures, we expect that the analysis of hospitalization data will provide accurate estimates of the incidence and prevalence of BD. Using the data from a national inpatient discharge database, the average annual incidence of BD in Poland was estimated at 0.5 per million persons, which is lower than that reported in other European countries.[23,24] The prevalence of BD in Poland was also lower than that reported for Turkey,[17] Iran,[18] northern Israel,[19] United States,[25] and European countries.[20,24] It appears that these differences between Poland and other countries may stem from environmental factors.

Our study revealed that BD was more often observed in women than men, although other studies reported various other distributions. Five nationwide surveys of BD have been reported in the literature, including studies from Iran, Japan, China, Korea, and Germany. The male to female ratios were 1.19, 0.98, 1.34, 0.63, and 1.40 to 1, respectively. Among the case series, 4 involved more than 200 patients (Turkey, Morocco, Tunisia, and the United Kingdom).[38]

In the above nationwide surveys of BD, the mean age at disease onset for Iran, Japan, China, Korea, and Germany was 26.2, 35.7, 33.8, 29, and 26 years, respectively,[38] which was substantially lower than the mean age of our patients (42.3 years). These age differences may be due to both environmental and genetic factors. One study suggested that a causative agent for BD might be widespread among children and give rise to BD only in genetically predisposed individuals infected in adulthood.[24] This speculative explanation requires that the distribution of the causative agent differs between the ethnic groups, and that behavior and social factors account for the differences between the sexes in different populations.[24]

The incidence rate of BD did not vary significantly between urban and rural regions in our study. Additionally, it was also reported that the observed prevalence in patients of Turkish origin living in Germany was similar to that reported for individuals living in western Turkey. This finding stands in contrast to the previous hypotheses of an environmental triggering factor and supports the role of genetic risk factors in the pathogenesis of BD.[20]

While genetic factors also appear to be involved in the development of certain features of BD, there is a consensus that as-yet unidentified environmental stimuli are required to initiate the disease process. The proposed exogenous triggers include both bacterial and viral infections, which may lead to dysregulation of the immune system and ultimately to phenotypic expression of the disease.[39]

Our study has several limitations. The analysis was based on hospital discharge records; therefore, it excluded patients who were treated only as outpatients. On the other hand, this type of systemic vasculitis may present with multiorgan involvement and may require advanced therapeutic and diagnostic procedures that can be done only in inpatient settings. We assumed that the diagnosis of BD in hospitals was based on the most current and widely used criteria. Although the study design may lead to inaccuracy in terms of the number of cases, we believe that the benefits of the analysis based on a nationwide hospital-based database balance this inaccuracy. Moreover, the first appearance of a BD diagnosis in the inpatient discharge database is not necessarily the date of the first diagnosis. This

inaccuracy may result in an overestimation of the number of incident cases. However, the long duration of follow-up in this study may minimize the overestimation.

Some of the above limitations may be overcome in future studies on vasculitis. Recently, a Polish center has developed an online electronic vasculitis database for online storage and analysis, which may improve the diagnosis and treatment of various types of vasculitis.[40]

In conclusion, BD has lower incidence and prevalence in Poland than in other European countries. Moreover, its incidence rate did not vary significantly between more urban and more rural regions of the country. BD was more often observed in women than in men. The occurrence of BD may be related to personal, infectious, environmental, or other unknown risk factors, but these observations require further research on this rare disease in Poland.

Contribution statement All authors contributed to study concept and design. All authors were involved in data collection, interpretation, and analysis. KK contributed to statistical analysis. NO-A coordinated funding for the project from the Medical University of Warsaw. All authors edited and approved the final version of the manuscript.

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